

# L’evoluzione del trattamento della GvHD acuta steroido-refrattaria: da immunosoppressione a immunomodulazione e riparazione tissutale

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Pavia

AIEOP
ASSOCIAZIONE ITALIANA EMATOLOGIA ONCOLOGIA PEDIATRICA

AIEOP MEDICI
LECCE, 12-14 ottobre 2026
HILTON GARDEN INN

# Disclosures

| Company name | Research support | Employee | Consultant | Stockholder | Speakers bureau | Advisory board | Other |
|---|---|---|---|---|---|---|---|
| Novartis | | | | | | x | |
| MSD | | | | | | x | |

# CLINICAL CASE

- 3-year-old boy — TDT
- HSCT from MUD 10/10
- BU+TT+FLU+ATG
- PBSC $CD34^+$ cells 9.05 x $10^6$/kg
- GvHD prophylaxis: MTX short term + CSA
- Engraftment PMN and PLT in D+17
- Complications: febrile neutropenia, grade 2 sec WHO mucositis, HHV6 reactivation

D26

Skin aGvHD
stage 1, grade I

MPDN 1 mg/kg/die (CR)

D63

Skin and gut aGvHD
stage 3, overall grade III

MPDN 2 mg/kg/die

D68

Gut aGvHD stage 4,
Overall grade IV

STEROID-REFRACTORY
aGvHD

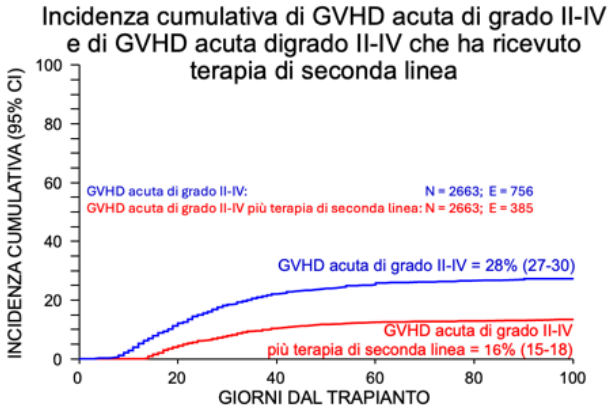


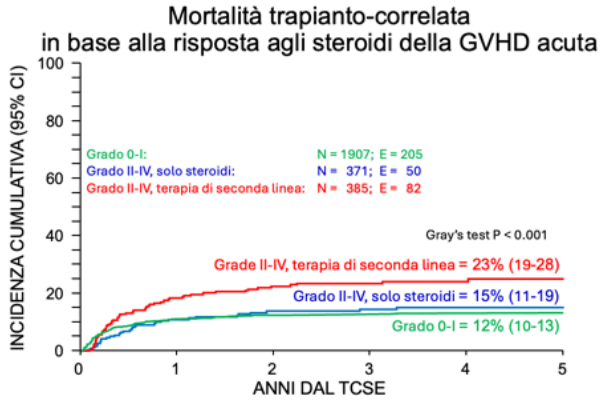
# Steroid Refractory-aGvHD

**Table 1. Criteria for corticosteroid-refractory and ruxolitinib-refractory acute GVHD**

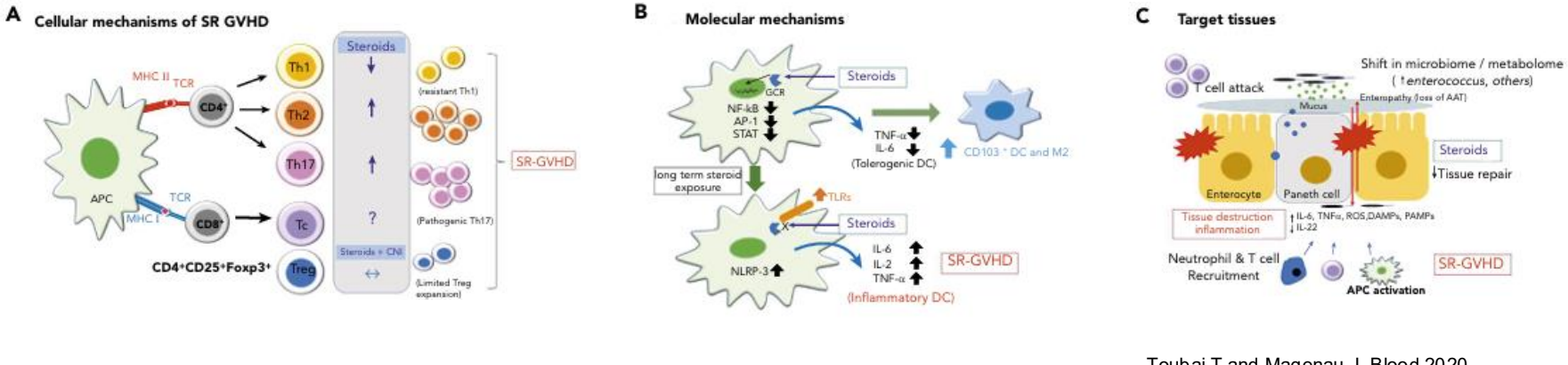
| Criteria |
|---|
| **Corticosteroid-refractory acute GVHD**<br>(1) Disease progression after 3 days of treatment with MP 2 mg/kg per day equivalent,<br>(2) Lack of improvement after 7 d of treatment with MP 2 mg/kg per day equivalent,<br>(3) Progression to a new organ after treatment with MP 1 mg/kg per day equivalent for skin and upper gastrointestinal GVHD, or<br>(4) Recurrence during or after a corticosteroid taper. |
| **Ruxolitinib-refractory acute GVHD**<br>(1) Progression of GVHD compared with baseline after ≥5 to 10 days of treatment with ruxolitinib, based either on objective increase in stage/grade or new organ involvement;<br>(2) Lack of improvement in GVHD (PR or better) compared with baseline after at least 14 days of treatment with ruxolitinib; or<br>(3) Loss of response, defined as objective worsening of GVHD determined by increase in stage, grade or new organ involvement at any time after initial improvement. |

Mohty *et al*, Blood 2020




Dati AIEOP, *unpublished*

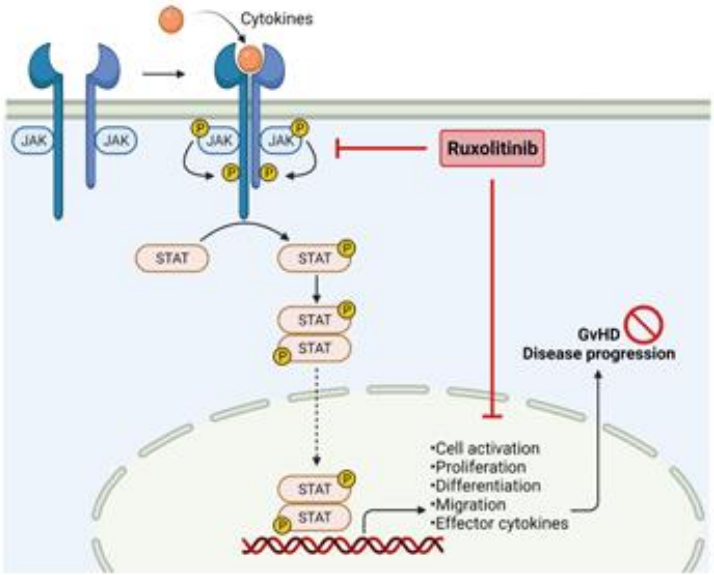



Toubai T and Magenau J, Blood 2020

# SR-aGVHD: not only steroid-resistant T cells

# If we only suppress the immune response, are we actually treating the disease?

# What's established: Ruxolitinib




Braun and Zeiser, Front Immunol 2021

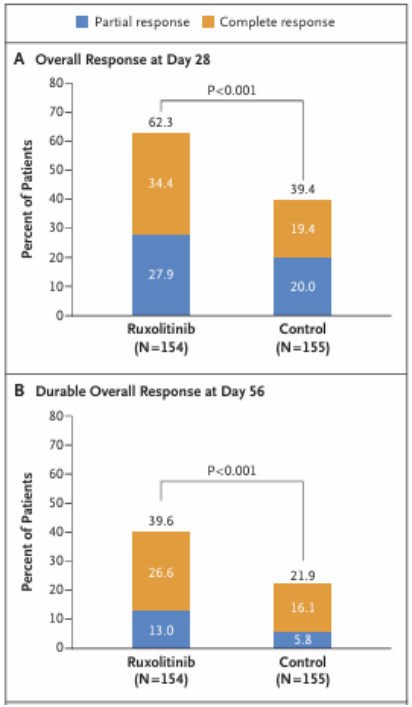
EBMT

**Prophylaxis and management of graft-versus-host disease after stem-cell transplantation for haematological malignancies: updated consensus recommendations of the European Society for Blood and Marrow Transplantation**

Olaf Penack*, Monia Marchetti*, Mahmoud Aljurf, Mutlu Arat, Francesca Bonifazi, Rafael F Duarte, Sebastian Giebel, Hildegard Greinix, Mette D Hazenberg, Nicolaus Kröger, Stephan Mielke, Mohamad Mohty, Arnon Nagler, Jakob Passweg, Francesca Patriarca, Tapani Ruutu, Hélène Schoemans, Carlos Solano, Radovan Vrhovac, Daniel Wolff, Robert Zeiser, Anna Sureda, Zinaida Peric

GITMO
GRUPPO ITALIANO PER IL TRAPIANTO DI MIDOLLO OSSEO, CELLULE STAMINALI EMOPOIETICHE E TERAPIA CELLULARE

## REACH 2

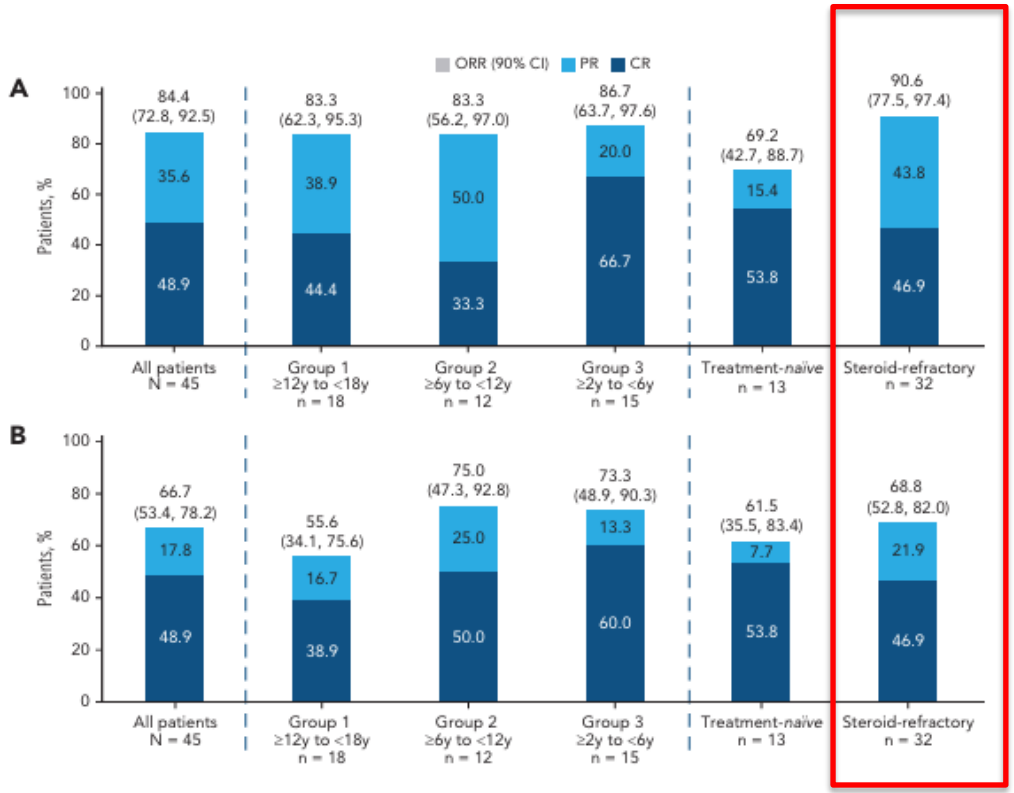



Zeiser et al, NEJM 2020

## REACH 4

G+28

G+56




Locatelli et al, Blood 2024



EGDS + colonscopy
aGvHD confirmed

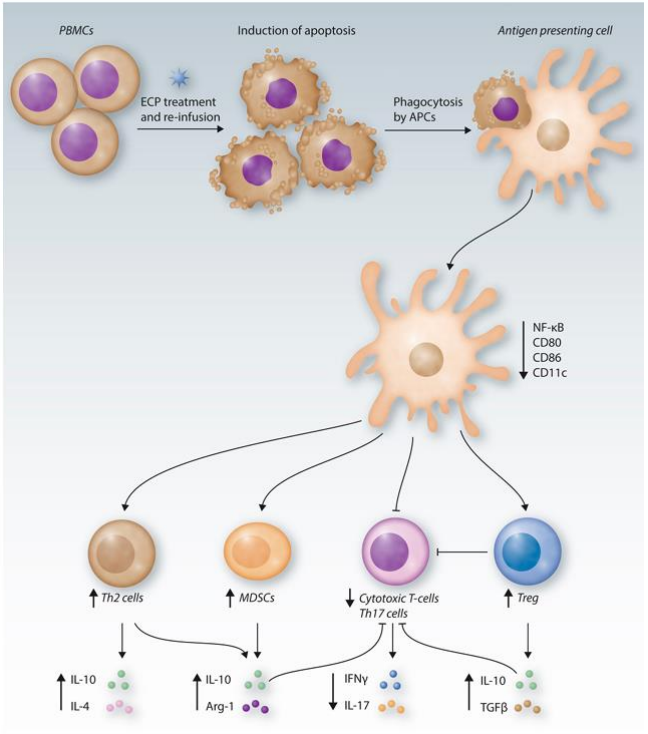
Ruxolitinib + ECP

Oral Budesonide

Supportive therapy
(octreotide, morfine)

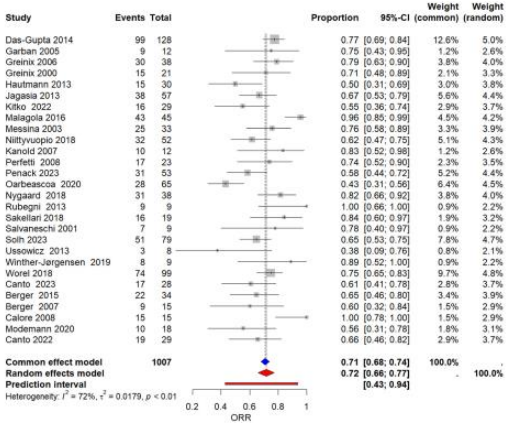
Infective complications
(MDR sepsis)

# Extracorporeal Photopheresis (ECP): immunomodulation withouth immunosuppression

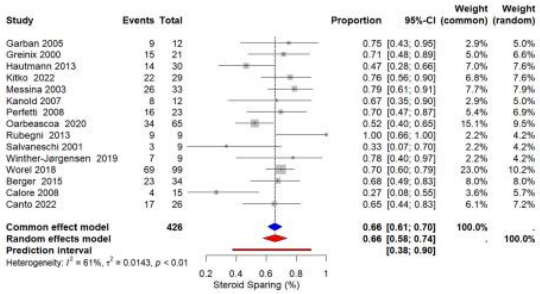



Braun and Zeiser, HemaSphere 2021

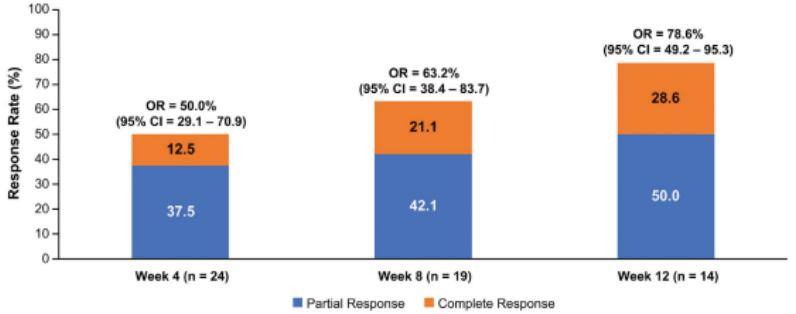
ORR




Steroid-sparing




Muhanna *et al* Front Immunol. 2025

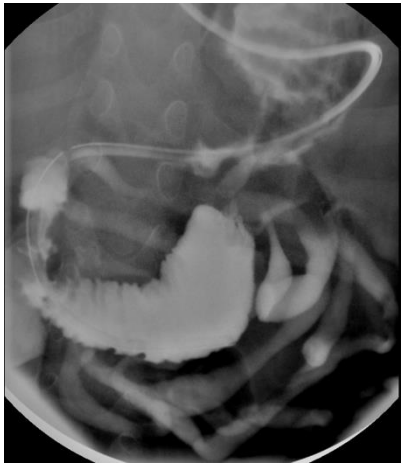



Kitko *et al* Transplantation and Cellular Therapy 2022

# 7 months post TCSE



Progressive intestinal damage: Duodenal stenosis



Failed recanalization attempt

# Ruxolitinib refractory-aGvHD

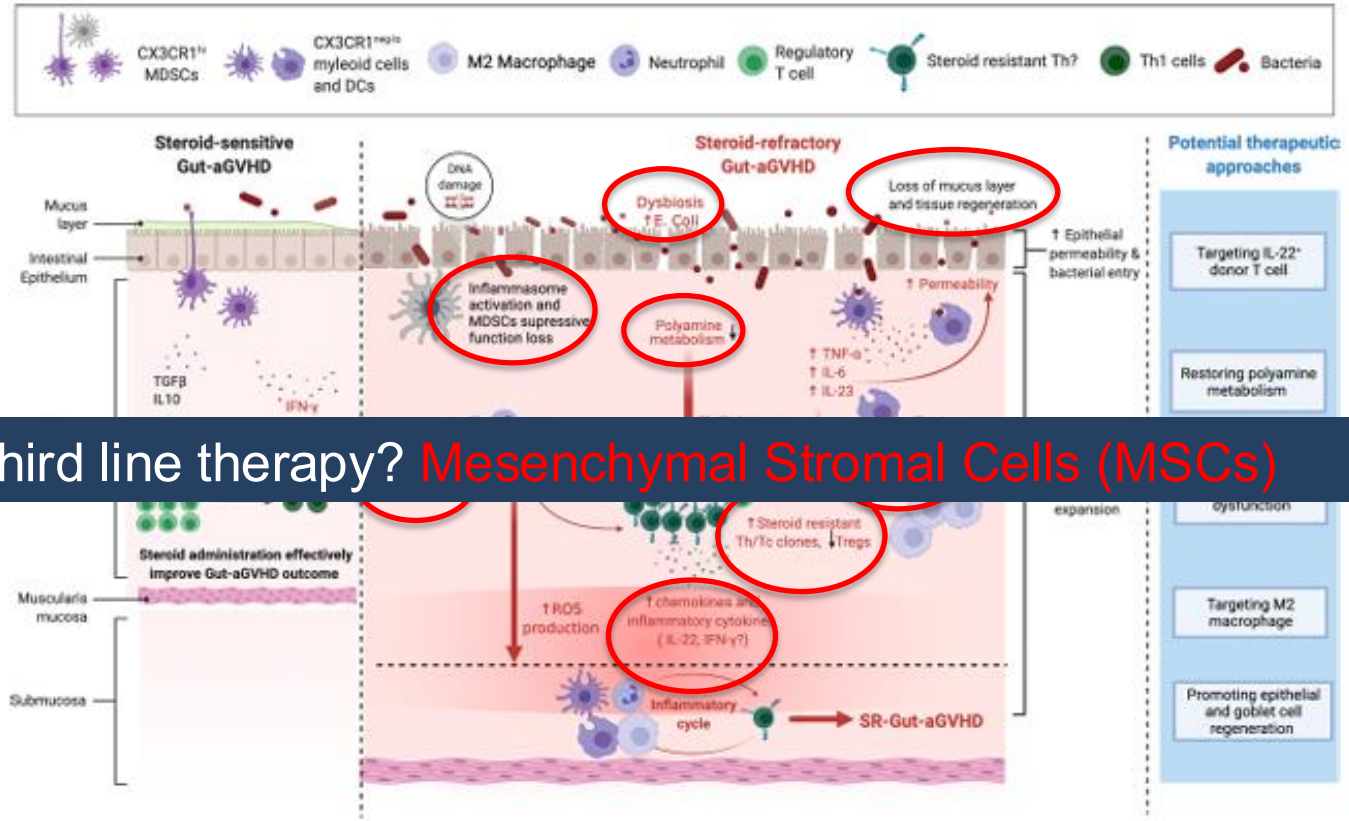
**Table 1. Criteria for corticosteroid-refractory and ruxolitinib-refractory acute GVHD**

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Mohty *et al*, Blood 2020

# What if the tissue has become the problem?




Which third line therapy? Mesenchymal Stromal Cells (MSCs)

Song et al, Frontiers in Immunol 2022

# MSCs: immunomodulation + tissue repair

| Endpoint | Remestemcel-L (n = 54), No. (%) * |
|---|---|
| **Day 28 response** | |
| Responder (OR = CR + PR) | 38 (70.4) |
| Complete response (CR) | 16 (29.6) |
| Partial response (PR) | 22 (40.7) |
| Very good partial response (VGPR) | 5 (9.3) |
| Nonresponder | 17 (31.5) |
| Mixed mesponse (MR) | 5 (9.3) |
| No response (NR) | 8 (14.8) |
| Progression | 4 (7.4) |
| CR + VGPR | 23 (42.6) |
| **Day 56 response** | |
| Responder (OR = CR + PR) | 32 (59.3) |
| Complete response (CR) | 17 (31.5) |
| Partial response (PR) | 15 (27.8) |
| Very good partial response (VGPR) | 6 (11.1) |
| Nonresponder | 12 (22.2) |
| Missing | 11 (20.4) |
| CR + VGPR | 23 (42.6) |

Kurtzberg J *et al*, BBMT 2020

No pooling
Pediatric patients with SR-aGVHD
2 x10$^6$/kg MSC twice/week x 4 weeks
(+ 4 weeks x responders)

**Table 3** Response status at day 28 after first administration of MSC-FFM and at last follow-up

Tomostrocel

| | *N* (%) | Day 28 | | | | | *P* | Last follow-up | | | | *P* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | CR | PR | NR | no report | OR | | CR | PR | NR | OR | |
| | | *N* (%) | *N* (%) | *N* (%) | *N* (%) | *N* (%) | | *N* (%) | *N* (%) | *N* (%) | *N* (%) | |
| All | 69 (100%) | 22 (32%) | 35 (51%) | 10 (14%) | 2 (3%) | 57 (83%) | | 42 (61%) | 17 (25%) | 10 (14%) | 59 (86%) | |
| Age | | | | | | | 0.717 | | | | | 1 |
| ≤18 y | 51 (74%) | 13 (25%) | 28 (55%) | 8 (16%) | 2 (4%) | 41 (80%) | | 33 (65%) | 10 (20%) | 8 (16%) | 43 (84%) | |
| >18 y | 18 (26%) | 9 (50%) | 7 (39%) | 2 (11%) | — — | 16 (89%) | | 9 (50%) | 7 (39%) | 2 (11%) | 16 (89%) | |

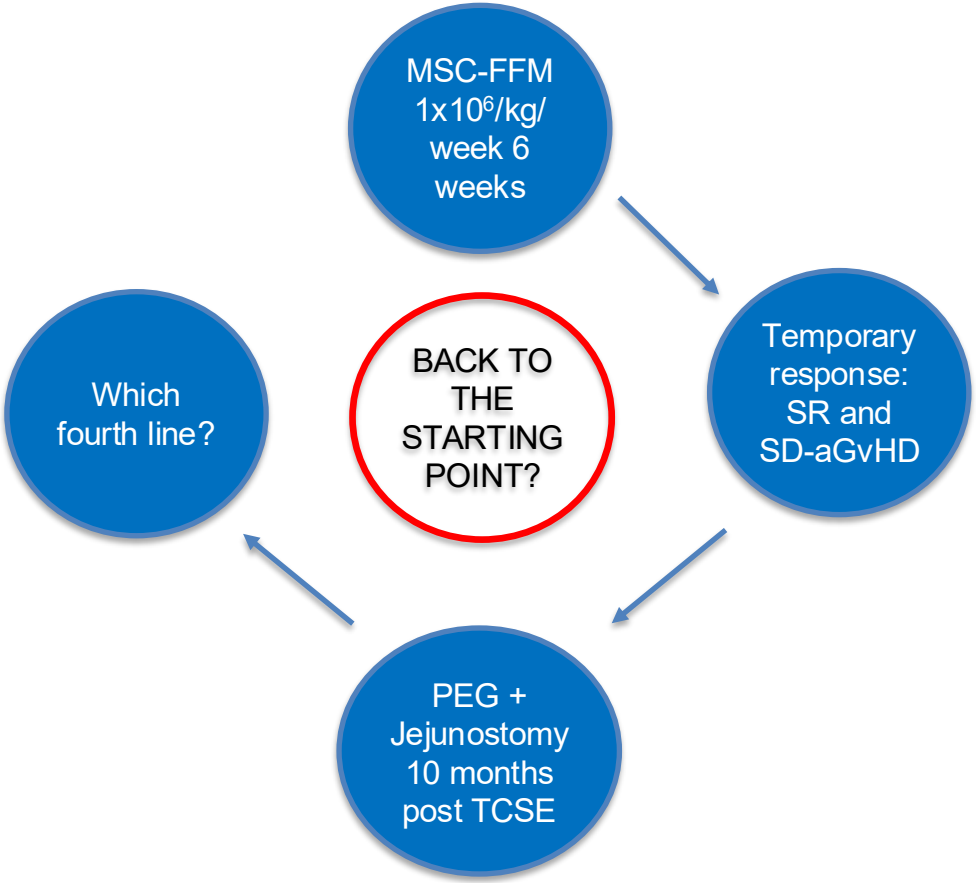
**SAME CELL TYPE ≠ SAME CELLULAR PRODUCT**

aGvHD in II-V therapy line
1 x10$^6$/kg MSC/week x 4 weeks

| | n | Response, n, (%) Overall response | Complete response | Partial response | No response |
|---|---|---|---|---|---|
| Total cohort | 140 | 88 (62.9%) | 31 (22.1%) | 57 (40.7%) | 52 (37.1%) |
| Patients with ruxolitinib pre-treatment | 76 | 49 (64.5%) | 14 (18.4%) | 35 (46.1%) | 27 (35.5%) |
| aGvHD grade prior to tomostrocel infusion | | | | | |
| **Grade I** | 1 | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 1 (100.0%) |
| **Grade II** | 27 | 20 (74.1%) | 13 (48.1%) | 7 (25.9%) | 7 (25.9%) |
| **Grade III** | 44 | 33 (75.0%) | 11 (25.0%) | 22 (50.0%) | 11 (25.0%) |
| **Grade IV** | 62 | 33 (53.2%) | 5 (8.1%) | 28 (45.2%) | 29 (46.8%) |

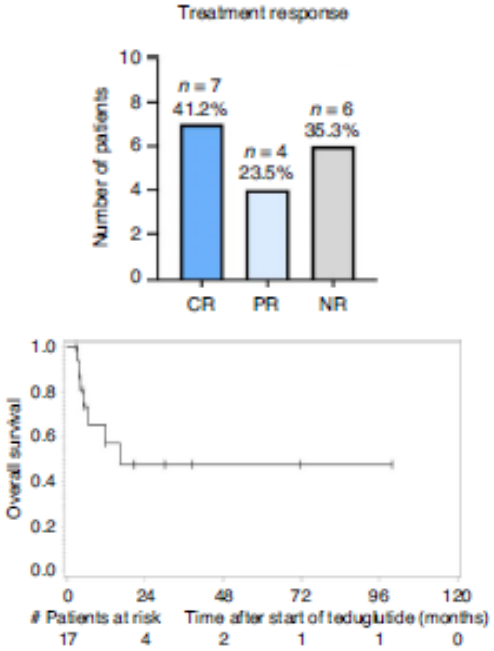
Volgelsang *et al*, Haematologica 2026




MSC-FFM
1x10⁶/kg/
week 6
weeks
Temporary
response:
SR and
SD-aGvHD
PEG +
Jejunostomy
10 months
post TCSE
Which
fourth line?
BACK TO
THE
STARTING
POINT?

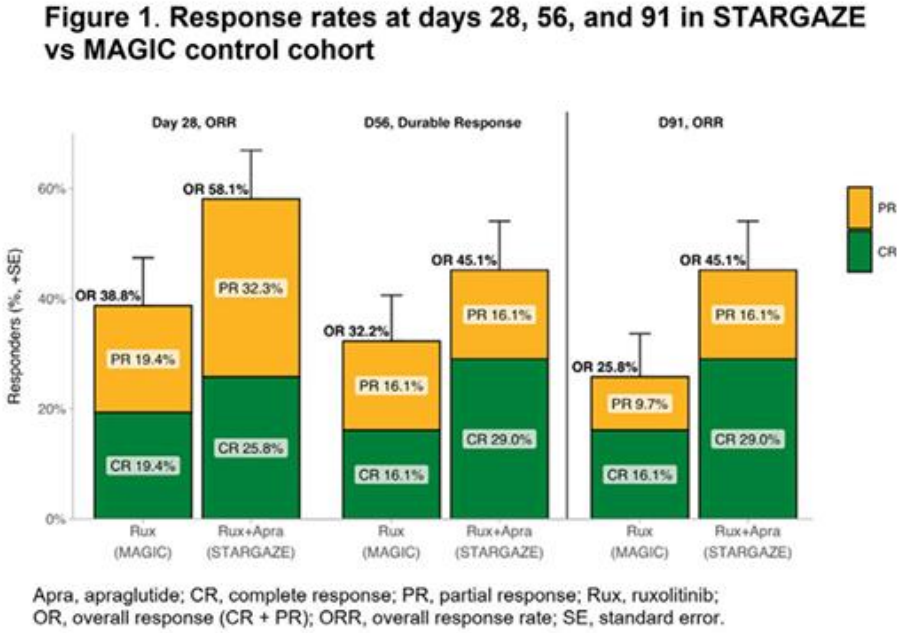
# Towards REGENERATION: Glucagon-Like-Peptide-2 agonists

## TEDUGLUTIDE




Brehm N et al, Bone Marrow Transplant 2025

## APRAGLUTIDE

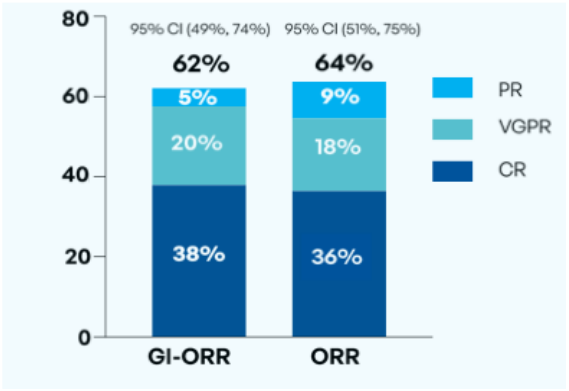


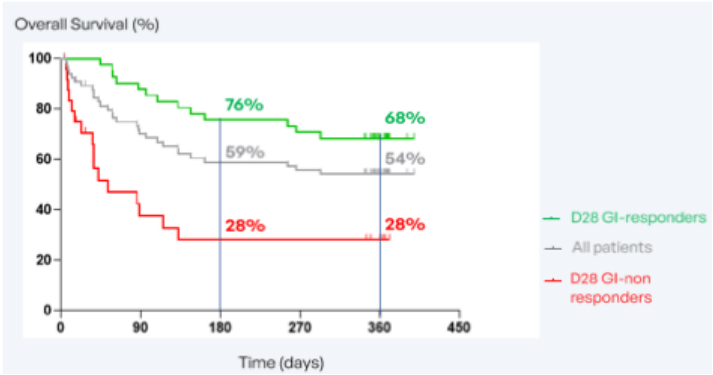

Zeiser R et al, Transplant Cell Therapy 2025

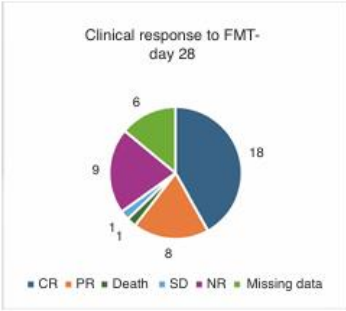
# RESTORING THE MICROBIOME: FMT

## STUDIO ARES MAAT013

D28



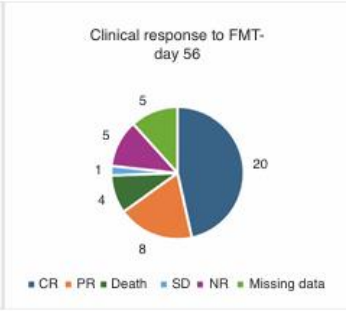




**Table 2.** Colonization status by drug-resistant bacteria/fungi and *C. difficile*.

| **Colonization status N (%)** | |
|---|---|
| **Prior to FMT** | |
| Drug-resistant bacteria | 17 (36.2%) |
| Drug-resistant bacteria and *C. difficile* | 1 (2.1%) |
| Drug-resistant bacteria and fungi | 4 (8.5%) |
| None | 25 (53.2%) |
| **Post FMT** | |
| Non-colonized with drug-resistant bacteria, fungi or *C. difficile* | 32 (74.4%) |
| Still colonized with drug-resistant bacteria, fungi or *C. difficile* | 10 (23.3%) |
| Died prior day 28 | 1 (2.3%) |
| Decolonization rate | 54.5% |
| Missing data | 4 (8.5%) |

Bilinki et al, Bone Marrow Transpl 2026

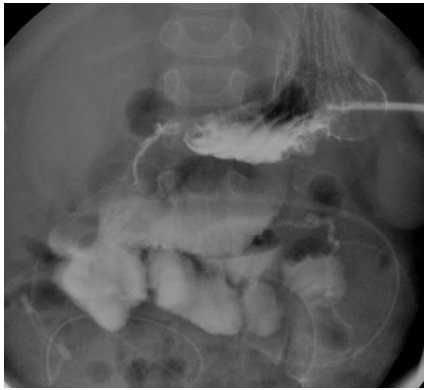

Pavia
Broni
Parma
Reggio Emilia
Modena
Bologna
Bologna
FMT

**16 months post TCSE**

**18 months post TCSE**

**23 months post TCSE**

FMT through jejunostomy → Progressive improvement → Successful recanalita-tion → Discharge



# Future prospectives

## IMMUNE MODULATION

ROCK1/ROCK2 inhibition (preclinical)

MSC secretome(preclinical)

Treg cell therapy

## TISSUE REPAIR

GLP-2 analogues

IL-22 / F-652 (1st line)

## MICROBIOME-BASED THERAPIES

FMT / MaaT013

## COMBINATION APPROACHES

CS + ruxolitinib

MSC + ruxolitinib

GLP-2 agonist + ruxolitinib

FMT + ruxolitinib

# Take home messages

- **SR-aGvHD is much more than simple T-cell resistance to steroids.**
  It results from a complex interplay between immune dysregulation, tissue injury, and microbiome alterations.

- **Treatment is shifting from immunosuppression towards immunomodulation.**
  Ruxolitinib and ECP are concrete examples of this transition.

- **The target is no longer the immune system alone.**
  MSCs, GLP-2 agonists, and microbiota-targeted therapies aim to restore tissue and intestinal homeostasis.

**We should not only suppress GVHD.**
**We should try to restore homeostasis.**

## PEDIATRIA 1 – ONCOEMATOLOGIA PEDIATRICA

Fondazione IRCCS Policlinico San Matteo

**Prof. Marco Zecca**

G Giorgiani
E Bergami
F Compagno
A Agostini
A Panigari
F Delle Cave
T Mina
V Sesenna
S Recupero
A Tolva
E Barbato
M Massa



### Cell Factory

P Comoli
A Moretta
S Basso

### Anti-leukemia Section

D Montagna
E Montini
M Tanzi
A Rumolo

### MSC Section

MA Avanzini
S Croce
E Lenta
C Valsecchi

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R Crocchiolo
C Del Fante
G Viarengo